Long-term effects of radiation therapy for a catecholamine-producing glomus jugulare tumor

Case report

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A 42-year-old woman presented with otorrhea 22 years after extracranial resection of a norepinephrine-secreting glomus jugulare tumor with intravascular embolization and radiation therapy to the intracranial portion of the tumor. Tumor growth was arrested and was associated with a decrease in blood and urine norepinephrine levels. Extensive evaluation of the otorrhea, including computed tomography-cisternography, gadolinium-enhanced magnetic resonance imaging, and arteriography showed marked diffuse necrosis of the temporal bone and skull base with limited tumor vascularity. Cerebrospinal fluid (CSF) collected from the right ear showed norepinephrine levels of 2975 pg/ml; plasma norepinephrine levels were normal. The precise site of CSF leakage could not be delineated. Exploration of the posterior fossa revealed a large dural defect at the anteromedial aspect of the petrous bone through which CSF flowed over the surface of the residual extradural glomus tumor. The defect was successfully sealed with a fascial patch. Postoperatively, CSF norepinephrine levels were normal and no further leakage was observed.

KEY WORDS • glomus jugulare tumor • norepinephrine • bone necrosis • radiation therapy • otorrhea • empty sella

GLOMUS tumors, first described by Rosenwasser in 1945, are rare. These benign, highly vascular, slow-growing tumors originate from the chief cells of the paraganglia in the adventitia of the dome of the jugular bulb, the auricular branch of the vagus nerve (Arnold's nerve), or the tympanic branch of the glossopharyngeal nerve (Jacobson's nerve). The tumor's appellation reflects its site of origin: glomus jugulare or vagal tumor. Glomus tumors occur predominantly in women aged 50 to 59 years. Only 1% to 3% are classified as functional (producing norepinephrine). This report describes a patient with profuse cerebrospinal fluid (CSF) otorrhea occurring 22 years after treatment of a glomus jugulare tumor by surgical removal of the cervical extension of the tumor and irradiation of the intracranial portion of the tumor. The long-term efficacy of radiation therapy in controlling tumor growth and catecholamine secretion was assessed with elaborate radiological studies, measurements of plasma and CSF catecholamine levels, and surgical exploration of the posterior fossa. We discuss the possible mechanism for the late onset of the CSF leakage and, in addition, the validity of normalization of urine or plasma norepinephrine levels after irradiation or surgery as an indication of successful treatment of the tumor.

Case Report

This 42-year-old woman was admitted to the Clinical Center at the National Institutes of Health in July, 1992, after a 3-month history of profuse right-sided CSF otorrhea. Her disease started in June, 1970, with episodic hypertension, headaches, palpitations, and an elevated urine catecholamine level. She had undergone an exploratory laparotomy in another hospital in an unsuccessful search for a pheochromocytoma. The patient had been admitted to the Clinical Center in the fall of 1970, when she was noted to have permanent palsies of the ninth, 10th, 11th, and 12th cranial nerves.
on the right side. The norepinephrine level in plasma from the right internal jugular vein was 37,000 pg/ml (normal range 350–700 pg/ml). A diagnosis of a norepinephrine-secreting glomus jugulare tumor with both cervical and intracranial extensions was made on the basis of radiological and arteriographic studies of the lesion (Fig. 1 left). During arteriography, the main arterial feeder of the tumor was visualized (Fig. 1). The extracranial portion of the tumor was resected, and the intracranial portion of the tumor received 5400 rad of radiation therapy. The cranial nerve palsies remained unchanged.

Follow-up evaluation included serial computerized tomography (CT) and magnetic resonance (MR) imaging, and measurements of urine and plasma catecholamine levels. Plasma norepinephrine levels remained moderately elevated (range 1108–1370 pg/ml), whereas the plasma epinephrine and dopamine content was normal. Urine levels of norepinephrine were normal to mildly increased (range 76–123 μg/dl; normal < 100 μg/dl), whereas urine levels of the catecholamine metabolites vanillylmandelic acid and metanephrine were normal. The patient was asymptomatic, except for occasional mild headaches and increasing hearing loss in her right ear. In 1986, she developed secondary amenorrhea and an empty sella syndrome confirmed on CT, presumably due to pituitary irradiation. In 1988, she had several brief episodes of CSF leakage from the right ear. Three months before the present admission, the CSF leakage became persistent and profuse.

Examination. Norepinephrine levels in CSF collected from her right ear were significantly elevated (2975 pg/ml), whereas plasma norepinephrine levels were normal (335 pg/ml). Iopamidol-enhanced CT-cisternography showed diffuse destruction of the right petrous bone and abundant contrast material in the mastoid cells (Fig. 2 left); however, the exact site of CSF leakage could not be determined. Gadolinium-enhanced MR imaging revealed the intracranial portion of the tumor, which extended from the nasopharyngeal mucosa to the anteromedial aspect of the petrous bone (Fig. 2 center). Right carotid arteriography demonstrated a faint tumor blush with persistent occlusion of the previously embolized arterial feeder of the tumor (Fig. 2 right).

Operation. Exploration of the posterior fossa revealed multiple dural attachments to the rough edges of the necrotic temporal and occipital bones. Intradural exploration revealed a deep round defect in the dura, measuring 7 mm in diameter at the anteromedial aspect of the petrous bone, just above the jugular foramen. Cerebrospinal fluid was leaking profusely through this dural opening and coming into contact with a brownish-red extradural tumor mass. A graft of fascia lata was sutured over the dural defect and further secured with fibrin glue. The rough edges of the necrotic temporal bone were also covered with fascia and fibrin glue.

Postoperative Course. External lumbar CSF drainage was continued for 7 days. The norepinephrine content of CSF was 335 pg/ml on the 4th postoperative day. The patient was discharged from the hospital, and no CSF leakage was observed during a 15-month follow-up period.

Discussion

Glomus jugulare tumor is a very rare tumor of the chief cells of the paraganglia; it has an incidence of one per 1.3 million population. The optimum management of glomus tumor with an intracranial extension is controversial. Partial surgical removal (with or without preoperative embolization and irradiation alone) are equally successful in controlling tumor growth. Advocates of surgery em-
Functional glomus jugulare tumor

Fig. 2. Studies performed in July, 1992. Left: Iopamidol-enhanced computerized tomography-cisternogram showing the intracranial portion of the tumor (small arrows), bone erosion of the right pyramid, and the possible site of cerebrospinal fluid leakage directly above the posterior part of the tumor (curved arrow). Contrast material is present in the mastoid air cells. Center: Contrast-enhanced magnetic resonance image demonstrating an enhancing mass in the same location (arrows) as shown left. Right: Right carotid arteriogram showing tumor blush similar to that shown in the postembolization study (Fig. 1 right) and permanent occlusion of the main tumor-feeding artery.

phosphatase the risk of radiation-induced brain necrosis and the possibility of tumorigenesis. Those advocating radiation as the primary therapeutic modality point to the high risk of new cranial nerve deficits, CSF leaks, and the perioperative mortality associated with surgery. Others have even questioned the necessity of any therapeutic intervention, noting the prolonged survival observed in untreated patients with glomus tumor. Pariesier reported that Rosenwasser's patient survived in stable condition from diagnosis in 1945 until 1987. A recent review by Springate and Weichselbaum of the available treatment modalities offers useful guidelines for treatment selection. The authors suggest that small intracranial tumors and tumors in the neck (Fisch's Grade A or B) should be surgically removed, whereas large intracranial tumors (Fisch's Grade C or D) are best managed by radiation therapy.

Although radiotherapy for glomus tumor is helpful, it is associated with various complications. An early complication is otitis and mastoiditis. Delayed complications include bone necrosis (1.7%), brain necrosis (0.84%), and secondary malignancy (0.28%), especially when high-dose radiation therapy is administered. Another complication of radiotherapy for tumors of the head and neck is pituitary-hypothalamic insufficiency. When our patient was evaluated 16 years after radiotherapy, she had an empty sella with hypogonadotropic hypogonadism, secondary amenorrhea, normal plasma prolactin, borderli ne but adequate thyroid function, and normal adrenal function. Her condition was presumably secondary to the radiotherapy, as she had borne a child 1 year before her glomus tumor was diagnosed and treated. Although a dose of 4500 to 5000 rad is considered to be without late complications, Guida, et al. have observed bone necrosis 19.6 years after a radiation dose of 3500 rad. The destruction of bone in glomus tumor by low-dose radiation therapy could be due to the relative resistance to radiation of osteoclasts, but not osteoblasts, and facilitated by the distant infiltration of the bone by the tumor. Patches of tumor inside the bone produce bone destruction by inducing an oblitative vasculitis and arteritis after irradiation.

Our patient demonstrated another complication of glomus tumor radiation: delayed dural necrosis with a CSF fistula and otorhea. This complication was probably related to both irradiation and destruction of the bone and dura by the residual tumor. Leakage of CSF is often an early complication of the surgical treatment of glomus tumor, but there is no report of a delayed CSF leak associated with treatment of glomus tumor. Prevention of radiation-induced bone necrosis is uncertain, but it has been suggested that low-dose irradiation (approximately 3500 rad in 200-rad fractions) seems to be effective in treating glomus tumors without causing bone necrosis. However, a recent report suggests that radiation doses of less than 4000 rad are ineffective in the treatment of glomus tumor.

Functional tumors, first described in 1962 by Glenner, et al., constitute only a small fraction of glomus jugulare tumors. These tumors produce norepinephrine, but not epinephrine, probably because of a lack of phenylethanolamine-N-methyl-transferase, the enzyme that converts norepinephrine to epinephrine. The current case illustrates the typical course of a functional glomus tumor with symptoms of a pheochromocytoma. Surgical removal of the easily accessible extracranial portion of the tumor with excision of the jugular vein followed by irradiation of the intracranial portion successfully controlled both the plasma norepinephrine level and the tumor growth. The observation of a high level of norepinephrine in the CSF bathing the tumor supports the observation of Brackmann, et al. that nonchromaffin paragangliomata chief cells survive radiation therapy. The low level of catecholamine secretory activity of the tumor was not sufficient to produce symptoms of catecholamine excess after partial removal of the tumor mass, interruption

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of the tumor’s blood supply via embolization, followed by irradiation. However, the local effects of norepinephrine on the brain are unknown.

In summary, the current report describes a late CSF leak complicating a glomus tumor treated 22 years before the radiation therapy. Despite residual local catecholamine secretion, radiation therapy controlled the tumor size and vascularity and prevented further systemic manifestations of catecholamine excess. Successful embolization of the main tumor-feeding artery was maintained, but the possible obliterative effect of irradiation should not be underestimated. Despite surgical obliteration of the site of the CSF leak, progression of radiation-induced bone and dural necrosis may manifest again in a similar way.

References

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